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Research context

An increasing number of people worldwide suffer from chronic illnesses, like type one diabetes mellitus (T1DM). All these patients expect and deserve an individualised and optimised treatment leading to an increase in quality of life, so research is needed to understand the underlying mechanisms of this disease. This will enable medical staff to prescribe evidence-based medicine. In T1DM, hyperglycemia and hypoglycemia are the unwanted complications of the disbalance between blood insulin and blood glucose concentrations ([BG]). Hypoglycemic events can be dangerous on short-term, but hyperglycemic events have an important impact on the long-term health, for example increasing the risk of cardiovascular complications. The mechanisms of these long-term effects are not fully understood yet. Consequently, cardiac function and structure needs to be investigated more in adolescents with T1DM.

Despite lack of evidence in adolescents with T1DM, literature shows that exercise seems to be beneficial for a lot of chronical illnesses. In adults with T1DM, physical exercise has been proven to be beneficial for promoting glycemic stability (Gulve, 2008). Despite this knowledge, patients with T1DM are often considered to be more sedentary or less active compared to their healthy peers. This can be accounted to several factors: fear of hypoglycemia, work schedule, loss of control over diabetes and low levels of fitness (Brazeau, Rabasa-Lhoret, Strychar, & Mircescu, 2008). Therefore, it is important to examine the physical fitness of an adolescent with T1DM. The role of physiotherapists in this domain is often underestimated. However, physiotherapists can examine the exercise tolerance of a patient by the execution of a cardiopulmonary exercise test (CPET). In addition, they are also experts in physical therapy and exercise scientists and are thus equipped to understand the ongoing processes in this disease. Physiotherapists therefore can play an important role in the management of this disease.

This study is part of a bigger research project, which investigates the effect of chronic illnesses on exercise capacity. In this study, we want to examine the cardiac structure and function. In addition, we want to investigate the exercise tolerance in adolescents with T1DM, compared with healthy controls. Furthermore, we want to examine if changes in cardiac function or structure can be related to several parameters of exercise tolerance. Finally, we are going to correlate parameters of glycemic control and lifestyle parameters, like physical activity, to significant

differences on trans-thoracic echocardiography (TTE) and CPET. In this way we attempt to find reasons for the changes seen in adolescents with T1DM.

The thesis is written by De Vriendt Friedelinde and Indesteege Jonas. Friedelinde has had a big account in the organisation of the study before the start of it. Both students had the same input for finding subjects. Jonas executed the test protocol in association with a student of the university of Maastricht. The research context and introduction were written by Jonas, revised by Friedelinde. The method section was written by Friedelinde and revised by Jonas. The statistics were executed by Jonas and checked by Friedelinde. Friedelinde wrote the results section. Both students shared an equal share in writing the discussion section. In this way, all sections were checked and amended by the other student.

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Manuscript

1. Abstract

Background: In adults with type 1 diabetes mellitus (T1DM), left ventricular diastolic dysfunction (LVDD) and exercise intolerance, and its relation to glycemic control, are well known complications. It remains uncertain whether those changes are already present in adolescents with T1DM.

Objectives: To examine exercise tolerance and cardiac function in adolescents with T1DM vs. healthy controls, and their interrelations. In addition, we aimed to study the relation between glycemic control and cardiac function/structure or exercise tolerance.

Participants: Fourteen participants between 12 and 18 years old with the diagnosis of T1DM and fourteen healthy controls were included.

Measurements: Exercise tolerance was evaluated by cardiopulmonary exercise test (CPET), with analysis of common CPET parameters. Furthermore, cardiac function and structure were examined through trans-thoracic echocardiography (TTE): Peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E/E' ratio, deceleration time of early filling, cardiac output (CO). The physical activity questionnaire for adolescents (PAQ-A) and an exercise diary were used to estimate physical activity levels. Information about glycemic control of the last two weeks and three months was gathered by reading the patient's own ambulatory blood glucose (BG) sensors.

Results: An increase in E ($p<0,05$) was found in T1DM, but other TTE parameters were preserved. Only the peak respiratory exchange ratio (RER_{peak}) and work rate efficiency (VO_2/W_{peak}) were significantly lower in T1DM as opposed to controls ($p<0,05$). Significant correlations ($p<0,05$) were found between RER_{peak} and PAQ-A ($r=-0.610$); as well between peak oxygen uptake (VO_{2peak}) and mean [BG] ($r=-0.799$) and between VO_2/W_{peak} and total time in hypoglycemic state ($r=0.808$).

Conclusion: Exercise tolerance and cardiac function were preserved in T1DM, but a higher mean [BG] seems to be correlated with a lower VO_{2peak}. A greater total time in hypoglycemic state was correlated with a higher VO_2/W_{peak}, indicating that glycemic control is related to exercise tolerance.

2. Introduction

Type 1 diabetes mellitus (T1DM), also known as juvenile-onset or insulin-dependent diabetes, is a form of diabetes mellitus that results from β-cell destruction, often mediated by an auto-immune reaction. Every year, the population of children with T1DM up to 14 years old in Europe is estimated to increase by 20.000. In Belgium, 15.9 per 100.000 children suffer from this disease (Patterson et al., 2014).

A lower aerobic capacity, quantified by a deteriorated peak oxygen uptake (VO_{2peak}) and heart rate reserve (HRR), is present in adolescents with T1DM when compared to healthy adolescents (Komatsu et al., 2005). However, when the healthy controls were compared to non-sedentary peers with T1DM, this difference diminished (Nascimento et al., 2017). This indicates that exercise training, or an increased physical activity, might prevent a lowering of the aerobic capacity in T1DM.

On the other hand, left ventricular diastolic dysfunction (LVDD) is a cardiovascular complication seen in a lot of adults with T1DM (de Ferranti et al., 2014). In this dysfunction, the heart cannot relax properly during the diastolic phase, causing less amount of blood flow into the left ventricle (LV). The cardiac output (CO) lowers and in extreme cases heart failure can emerge. Some studies suggest that these changes in heart structure also occur in younger subjects with T1DM. Trans-thoracic echocardiography (TTE) has revealed LVDD in some children with T1DM. Furthermore, the LV longitudinal and radial function showed impairments in asymptomatic children with T1DM with a normal LV ejection fraction (EF) (Altun et al., 2016). Alterations in LV size and longitudinal myocardial deformation can be present with a shift to circumferential shortening (Bradley et al., 2016; Hodzic et al., 2016).

The glycemic control seems to be related to cardiac structure and exercise tolerance. For example, in children with T1DM higher A1c concentrations in hemoglobin ([hbA1c]) will lead to a lower VO_{2peak} (Fintini et al., 2012). Furthermore, literature suggests that a decreased CO is related to a greater insulin resistance (Moser et al., 2017; Niedzwiecki et al., 2017; Wilson et al., 2017). In addition, higher levels of HbA1c in adults with T1DM were correlated with a deterioration of LV systolic function (N. H. Andersen, Hansen, & Christiansen, 2007). In brief, there is an increasing amount of evidence showing a poor glycemic control causes reductions in exercise tolerance

and/or a deterioration of cardiac function, at least in adults. However, this remains to be studied in adolescents with T1DM. Moreover, it remains to be examined whether exercise tolerance is related to such cardiac changes in adolescents with T1DM.

The aim of this study is fourfold 1) to examine differences in exercise tolerance or cardiac function between adolescents with T1DM and healthy controls, 2) to find correlations between glycemic control and cardiac structure/function, 3) to investigate relations between glycemic control and physical fitness, and 4) to examine relations between physical fitness and cardiac structure/function.

The following research questions can be extracted from the above stated: 'Do deviations of cardiac function occur during a maximal exercise tolerance test in adolescents with T1DM?' Additionally, 'Are there any correlations between the functioning of the heart, the exercise capacity and/or the glycemic control in this population?'

We hypothesize that adolescents with T1DM will have an altered exercise tolerance and a changed cardiac function/structure seen on TTE, compared to their healthy peers. We also presuppose that the glycemic control and physical level of activity are related to exercise tolerance and cardiac function in adolescents with T1DM.

3. Methods

a. Study design

This observational pilot study, executed in the Jessa Hospital (Hasselt, Belgium), examined the relation between cardiac function, parameters of glycemic control and the cardiopulmonary exercise capacity in adolescents with T1DM. Cardiac function was assessed by TTE. In addition, participants executed a maximal cardiopulmonary exercise test (CPET) and filled out a physical activity questionnaire for adolescents (PAQ-A).

b. Participants

Fourteen Caucasian adolescents (aged 12-18 years, nine boys and five girls) with T1DM (based on American Diabetes Association (ADA) criteria) were included. Besides being diagnosed with T1DM, these adolescents were free from any chronical illnesses or impairments hindering exercise or physical activity. The latter were screened by a pediatrician. The participants were recruited from the Pediatrics Department of Jessa Hospital, Hasselt. All subjects and their parents or legal guardians received information (oral or written) about the aim and protocol of the study. They gave their signed and written informed consent prior to participating in the study. The control group was extracted from data from the unpublished study by Franssen et al. and matched with the T1DM group based on gender, age and body mass index (BMI).

c. Measurements

All participants' glycemic control was evaluated through the patient's own continuous glucose monitoring system (FreeStyle Libre®or Enlite® sensor) for fourteen consecutive days and three months, prior to the study screening day. The screening involved a clinical evaluation for the assessment of general health, current glycemic control based on [HbA1c] and daily [BG] and maturation based on Tanner. This evaluation was performed by a pediatrician. The participants then underwent a bio-electrical impedance test to evaluate body composition, a maximal CPET for examination of physical fitness and cardiovascular response and a TTE for the screening of cardiac function.

Auxological parameters

Examination of puberty stage: The Tanner stage, which defines physical features of development based on external primary and secondary sex characteristics, was determined according to observation by a pediatrician (Marshall & Tanner, 1969, 1970).

Body composition analysis: The body height was measured to the nearest 0.001m using a wall-mounted "Harpenden" stadiometer, with the participants barefoot. The body mass was measured with an electronic weighting scale to the nearest 0.1 kg with subjects in underwear. Subsequently, BMI was calculated from the ratio of weight (in kilograms) to height (meters squared) (BMI=kg/m²). An age-adjusted BMI and height was formed by calculating the SDS-score of both values. Whole-body fat mass and lean tissue mass were estimated by use of a Bodystat 1500 MDD device.

Assessment of cardiac structure/function

All participants underwent a standardized transthoracic echocardiographic (TTE) examination using a commercial ultrasound system (Vivid E9, GE Health Medical) and a phased array matrix transducer (GE MS5-D probe, 1.5 - 4.6 MHz, Vivid E9 ultrasound system, GE Health Medical), executed by a trained researcher. Two-dimensional (2-DE) and motion mode (M-mode) TTE parameters were obtained with the subjects lying in the supine or left lateral semi recumbent position; standard parasternal and apical views were used, as described before in research (O. S. Andersen et al., 2017). LVDD was assessed using transmittal inflow patterns, LV EF, mitral annulus velocity, left atrium (LA) diameter. Transmittal inflow patterns were obtained using pulsed-wave Doppler TTE. Peak early (E) and late (A) diastolic velocities, the E/A ratio and the deceleration time of early filling velocity were determined using the apical 4 chamber views. The EF was measured using apical four or two chamber views and determined using the biplane modified Simpsons method. The mitral annulus early diastolic velocity (e') and late diastolic velocity (a') were determined using four chamber views at septal and lateral mitral annulus and the E/e' ratio was assessed. All TTE and Doppler assessments and analyses were stored digitally until analysis using the EchoPAC software (GE Health Medical).

Maximal cardiopulmonary exercise testing

After the assessment of [BG] by the patient's own ambulatory device (FreeStyle Libre®, Enlite® or Dexcom® sensor), a maximal CPET up to volitional exhaustion on an electronically braked cycle ergometer (Ergofit GmbH & Co, Pirmasens, Germany) was executed, according to clinical guidelines (Fletcher et al., 2001). The test was postponed when [BG] was below 80 mg/dl or above 250 mg/dl before starting the test, tested with the patient's own continuous glucose

monitoring system or a BG monitor (Komatsu et al., 2005; Moser et al., 2017; Turinese et al., 2017). On the morning of each test day, a gas- and volume calibration was executed in the testing room. Participants were instructed to have an unstandardized meal and insulin bolus at least 120 minutes before the start of the test (Komatsu et al., 2005; Wilson et al., 2017). First, the participants had to rest for one minute while seated on the bike ergometer, followed by a warm-up of one-minute cycling without resistance. The test protocol initiated at 30 Watts (for participants up to 16 years) or 40 Watts (for participants 16-18 years), the load increasing every minute (by 15 Watts for participants up to 16 years, and by 20 Watts for participants 16-18 years). A cycling frequency of 70 revolutions per minute (rpm) had to be maintained. All participants were verbally encouraged during exercise testing to achieve a maximal exercise test. The test was ended when pedal frequency fell under 60 rpm or other symptoms occurred. It was considered maximal when respiratory exchange ratio (RER) > 1.1 and an experienced tester confirmed the execution of a maximal test. Participants were asked to state what the reason of having to end the test was (based on fatigue, dyspnoea or leg muscle pain). By use of continuous pulmonary gas exchange analysis (Jaeger MasterScreen, CPX Metabolic Cart, CareFusion GmbH, Germany), oxygen uptake (VO_2), carbon dioxide output (VCO_2), breathing frequency (BF), expiratory volume (VE), RER, equivalents for oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2), tidal volume (Vt), respiratory rate (RR), end-tidal oxygen ($PETO_2$) and carbon dioxide ($PETCO_2$) pressure were collected breath-by-breath and averaged every ten seconds. The timing of the highest VO_2 from the raw data was used to collect the other peak exercise parameters. Heart rate (HR) was monitored using a 12-lead electrocardiogram (ECG, Cardiosoft Diagnostic System, GE Healthcare, Little Chalfont, UK). The signal was windowed into ten seconds blocks each and then averaged. From this parameter the oxygen pulse (VO_2/HR) was calculated. The oxygen uptake efficiency slope (OUES) was calculated using all exercise data by a linear least square regression of VO_2 on the logarithmic of VE (Bongers et al., 2016). The first ventilatory threshold (VT1) was determined using the V-slope method (Wasserman, Stringer, Casaburi, Koike, & Cooper, 1994). The second ventilatory threshold (VT2) was determined using the VE vs. VCO_2 plot, at the point where VE increased out of proportion to VCO_2 and expressed in ml/min and in percentage of VO_{2peak}. Both ventilatory thresholds were determined by the same researcher in all the cases to minimize possible inter-rater differences. In addition, maximal cycling power

output (W_{peak}) was documented. Relative load (W/kg bodyweight) and work rate efficiency (VO_2/W_{peak}) were derived from the above-mentioned parameters. A selection of these parameters reflects ventilatory function (VE_{peak}, lowest VE/VO2, lowest VE/VCO2, Vt_{peak}, Vd/Vt_{peak}, $PETO_{2peak}$, $PETCO_{2peak}$, BF_{peak}), cardiac function (HR_{peak}, VO_2/HR_{peak}), physical fitness (VO_{2peak}, W_{peak}) and lactate metabolism (VT1 and VT2).

Assessment of physical activity

The participants filled out the PAQ-A, specifically designed and validated for Dutch speaking adolescents (Bervoets et al., 2014). Furthermore, they all received a physical activity diary where they wrote down what type of exercise they executed for a total duration of two weeks, prior to the day of the exercise test.

Assessment of glycemic control

Participants continuously monitored their [BG] (for patients wearing an insulin pump: Enlite® BG sensor (Medtronic), for patients administering insulin injections: FreeStyle Libre® sensor (Abbott)). When possible, Two-week and three-month data were extracted from the patient's devices.

Primary outcome measures

Cardiac function.

Secondary outcome measures

Participant's clinical characteristics, body composition, physical fitness, parameters of glycemic control, physical activity and possible relations between the previously mentioned parameters.

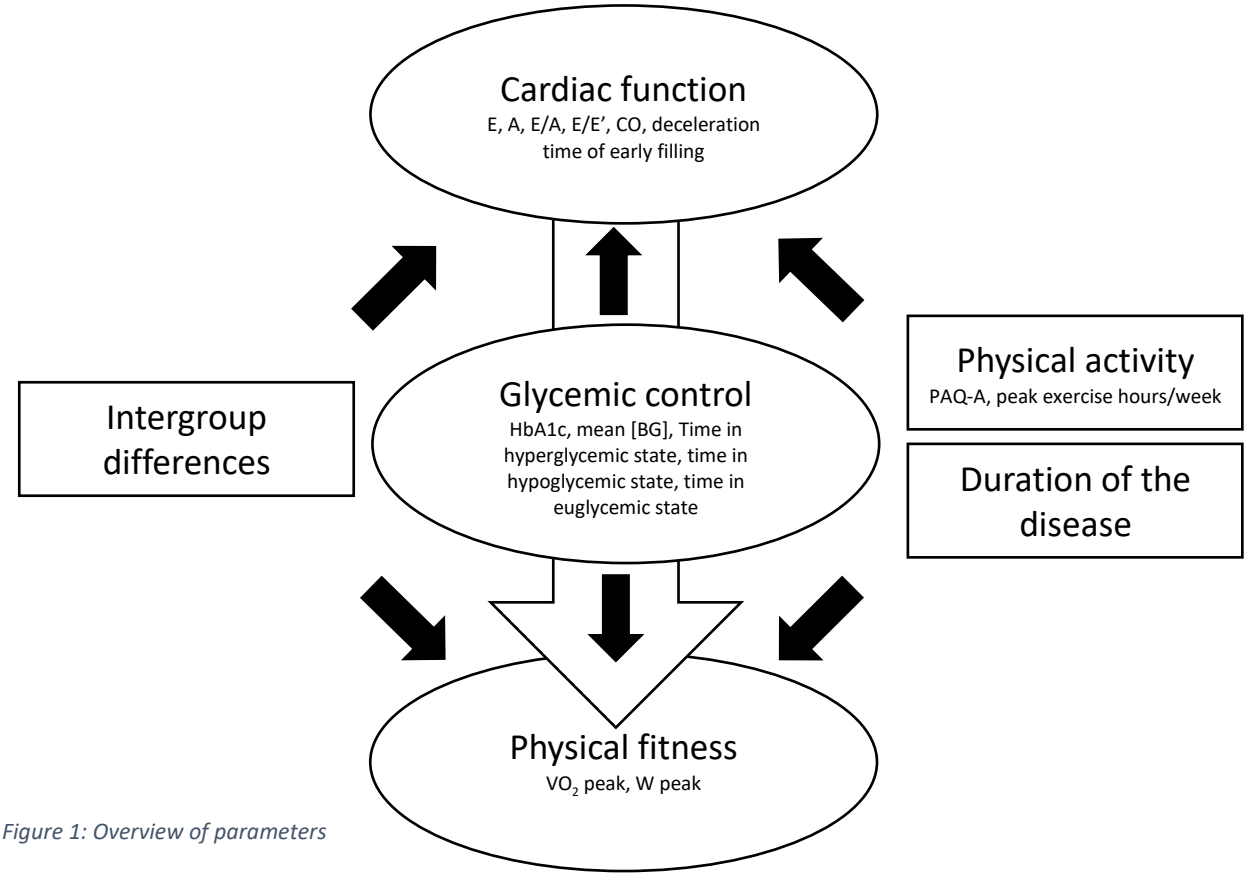


Figure 1: Overview of parameters

d. Medical ethics

The study was approved by the Committee of Medical Ethics of the University of Hasselt, as well as the committee of the Jessa Hospital, Hasselt. All the participants, and their parents/legal guardians, were informed about the aim, nature and risks/benefits of this study, and were requested to sign an informed consent.

e. Data analysis

The statistical analyses were carried out in SPSS 25.0 (IBM, Chicago, IL, USA). Power analyses were performed through G*Power (Faul, Erdfelder, Buchner, & Lang, 2009). A p-value <0.05 (2-tailed) was considered as statistically significant. Normality of data were analysed by Shapiro-Wilk tests, homoscedasticity through the Levene's test. Then, data were expressed as mean ±SD. Parametrical data were put through a one-way ANOVA test, non-parametrical data through the Mann-Whitney U or Welch test. Relations between parameters were examined by Pearson (in case of continuous data) or Spearman (in case of ordinal/nominal data) correlations.

4. Results

a. Subject characteristics

Fourteen patients with T1DM were included in the study. All fourteen participants with T1DM were matched with controls (CON) based on gender, age and BMI; this made a total of 28 participants. The subject characteristics, consisting of gender proportion, mean age, Tanner stage, body weight, height, BMI and body fat percentage were comparable between groups (p>0,05, *details in Table 4 in appendix, values presented as mean ± SD*). Furthermore, Scores on PAQ-A did not differ significantly (p>0,05) between groups (*see Table 4*). All Tanner stages (ranging from 1 to 5) were represented in the sample, with one subject in the T1DM group not being classified at the moment of analysis. Ten patients with T1DM completed all analyses. Four participants only completed the CPET, self-reported exercise and glucose control but did not undergo TTE, due to practical considerations. Furthermore, we received data from 10 participants' continuous glucose monitoring systems. Two different types of sensors were used, we therefore could not evaluate all the parameters in all the T1DM participants.

b. Cardiopulmonary exercise capacity

Table 5 (*Appendix*) shows the results of the maximal exercise capacity test, values are presented in mean ± SD. RER_{peak} was significantly lower (p<0,05) in T1DM vs. CON (1.15 ± 0.08 vs. 1.24 ± 0.06. The maximal oxygen uptake / work rate ratio was significantly higher (p<0,001) in T1DM as opposed to CON (13.95 ± 1.10 vs. 11.91 ± 0.73). The first ventilatory threshold was significantly

Table 1
Relevant differences T1DM vs controls

Parameters	Controls (n= 14)	T1DM (n=14)	P-value	Power
RER_{peak}	1.24 ± 0.06 [1.21;1.27]	1.15 ± 0.08 [1.11;1.20]	**0.004***	0.90
VO_2/W_{peak} (ml/min*W)	11.91 ± 0.73 [11.48;12.33]	13.95 ± 1.10 [13.32;14.59]	**<0.001***	1.00
VO_2 VT1 (ml/min)	1203.55 ± 298.61 [1002.94;1404.15]	1410.25 ± 394.26 [1195.75;1660.75]	**0.026***	0.31
E (cm/sec)	79.20 ± 9.65 [72.30;86.10]	93.00 ± 16.95 [80.87;105.13]	**0.031***	0.54

Abbreviations: RER_{peak} = respiratory exchange ratio at peak exercise, VO_2/W_{peak} = ratio of oxygen uptake to cycling load at peak exercise, VO_2 VT1 = oxygen uptake at first ventilatory threshold and E = peak early diastolic velocity

higher (p<0,05) in T1DM vs. CON (1410.25 ± 394.26 vs. 1203.55 ± 298.61). All of the other tested CPET parameters did not differ significantly between the groups (p>0,05).

c. Cardiac structure and function

E was significantly higher in T1DM vs. CON (93.00 ± 16.95 vs. 79.20 ± 9.65) respectively (p<0,05, *Table 6, Appendix*). None of the other parameters extracted from TTE showed significant differences between groups (p>0,05).

d. Relation between aberrant parameters

Relation between glycemic control or physical activity and exercise tolerance

Mean [BG] over three months was significantly correlated to two parameters of exercise tolerance. More specifically VO_{2peak} (r=-0.799, p=0.017) and peak power output (r=-0.772, p=0.025) had a significant relation to mean [BG] over three months (*Figure 2*) (*Table 7, Appendix*). Physical activity showed no significant relation to exercise tolerance.

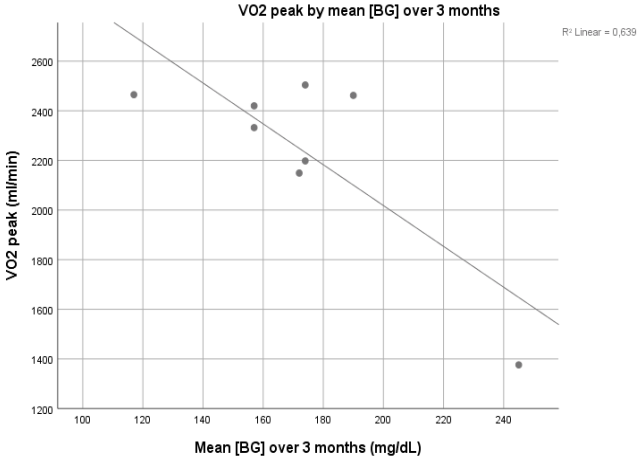
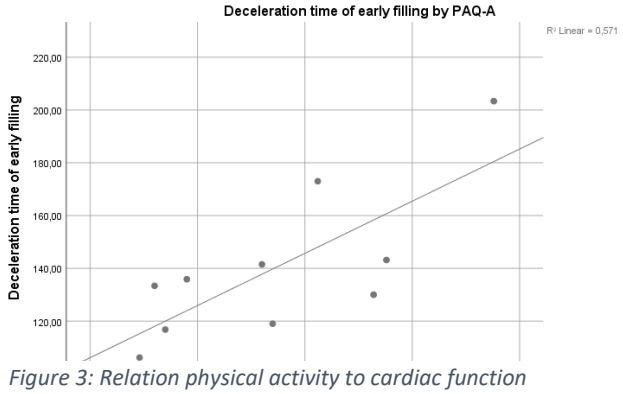


Figure 2: VO_{2peak} by mean [BG] over 3 months

Relation between glycemic control or physical activity and cardiac function

The results of our analyses showed no relation between glycemic control and cardiac function. The PAQ-A however was significantly correlated with deceleration time of early filling (r=0.756, p=0.011) and LA diameter (r=-0.786, p=0.007) (*Figure 3*) in T1DM patients but not in healthy controls (*Table 8, Appendix*).



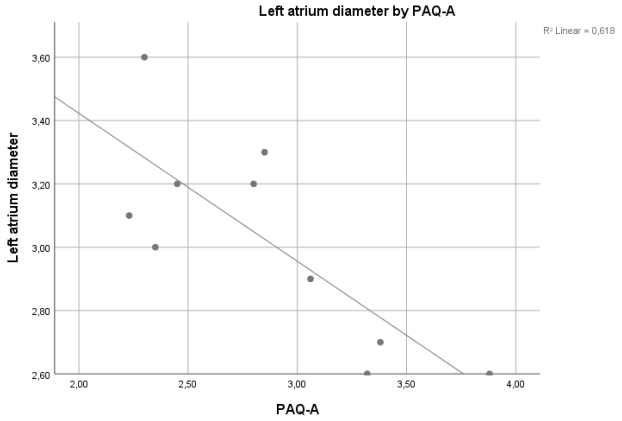


Figure 3: Relation physical activity to cardiac function

Relation between exercise tolerance and cardiac function

The E/A ratio was the only parameter of cardiac function which was found to be related to exercise tolerance. E/A seemed to have a strong significant correlation to VO_{2peak} (r=0.808, p=0.005) (*Figure 4*) and the peak power output (r=0.810, p=0.005) (*Table 9, Appendix*). No other relations between exercise tolerance and cardiac function could be found.

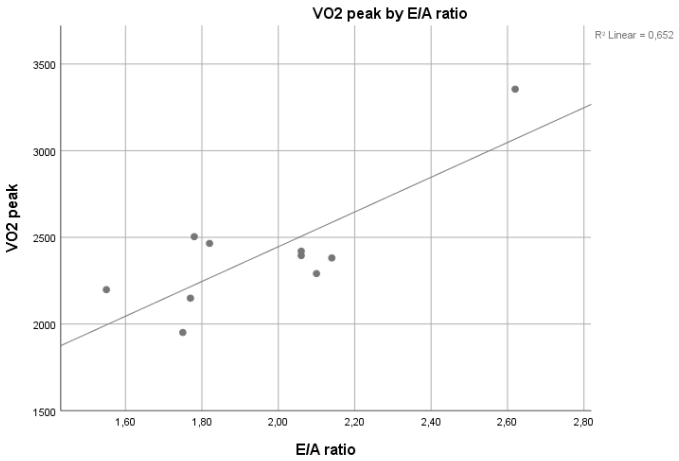


Figure 4: VO_{2peak} by E/A ratio

Duration of the disease

The duration of the disease or the time since diagnosis was another parameter investigated to see if any significant correlations could be found with outcome parameters of the CPET or TTE (*table 10, Appendix*). The duration of the disease showed a significant negative correlation with work load in T1DM subjects (r=-0,544, p=0,040). VO_{2peak} and VCO_{2peak} were also found to be related with duration of the disease: (r=-0,658, p=0,011) and (r=-0,598, p=0,024) respectively (*Figure 5*). The oxygen pulse and the duration of the disease showed a significant negative correlation (r=-0,665, p=0,009), so did the second ventilatory threshold, relative VO_2 and relative workload (r=-0,578, p=0,049), (r=-0,777, p=0,001), (r=-0,771, p=0,001) respectively. The duration of the disease was significantly correlated with the ejection fraction. None of the other TTE outcomes were correlated significantly (p>0,05). Age and the duration of the disease were also not significantly correlated (p=0,242).

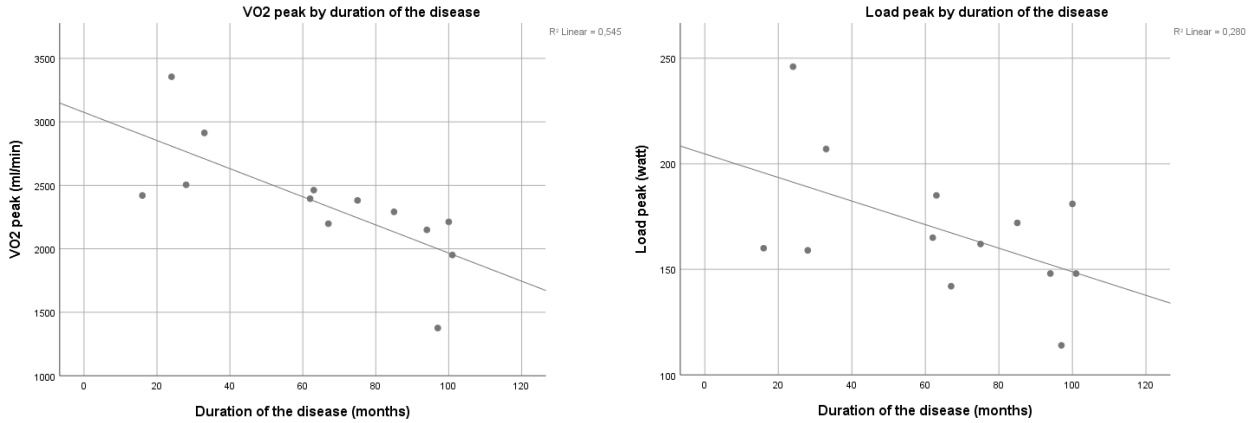


Figure 5: Duration of the disease

Relation between [BG] before maximal exercise and CPET parameters

We also examined the possible relation between [BG] before starting the test and the outcome parameters of the maximal CPET, to see if this could have an influence on outcome. No statistically significant correlations were found between [BG] before starting the maximal CPET and outcome parameters from this testing protocol (see table 6, appendix).

Supplementary correlations

The following correlations were found to be of statistical significance (*Table 12, Appendix*): The outcomes on the PAQ-A were found to be significantly and negatively correlated with the RER_{peak} (r=-0,620, p=0,018) (*see figure 6*). Total time in hypoglycemic state (three months) and work rate efficiency showed a significant positive correlation (r=0,808, p=0,028) (*figure 6*).

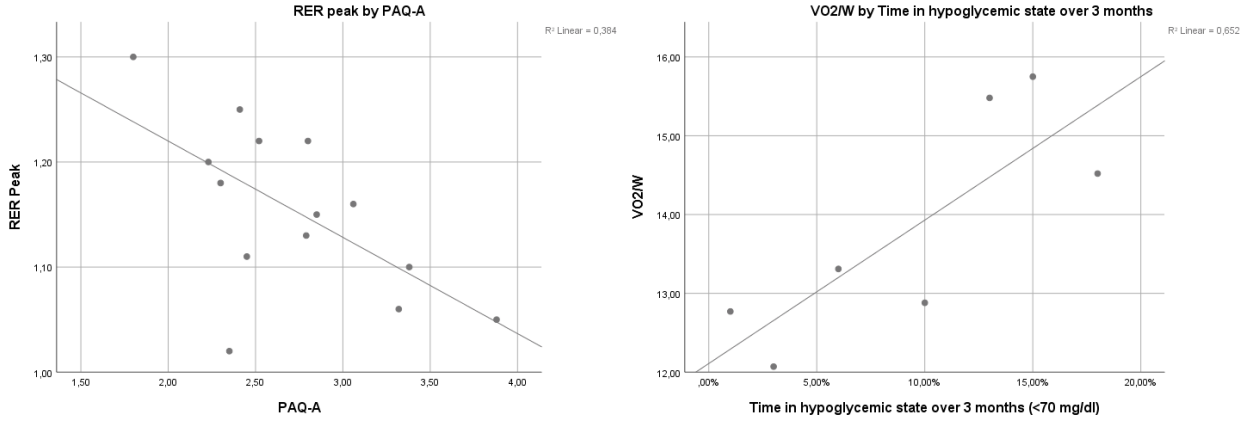


Figure 6: Supplementary correlations

Table 2
Relevant correlations

Parameter 1	Parameter 2	Correlation coefficient	P-value	Power
VO_{2peak} (ml/min)	E/A ratio	0.808	0.005	0.97
$Load_{peak}$ (W)	E/A ratio	0.810	0.005	0.97
$VO_{2\ peak}$ (ml/min)	Mean [BG] over 3 months (mg/dl)	-0.799	0.017	0.76
$Load_{peak}$ (W)	Mean [BG] over 3 months (mg/dl)	-0.772	0.025	0.82
Deceleration time of early filling (ms)	PAQ-A	0.756	0.011	0.89
LA diameter (mm)	PAQ-A	-0.786	0.007	0.94
Duration of the disease (months)	$Load_{peak}$ (W)	-0.544	0.040	0.61
Duration of the disease (months)	VO_{2peak} (ml/min)	-0.658	0.011	0.011
Duration of the disease (months)	VO_2/HR_{peak}	-0.665	0.009	0.86
RER_{peak}	PAQ-A	-0.620	0.018	0.77
VO_2/W_{peak} (ml/min*W)	Total time in hypoglycemic state over 3 months (%)	0.808	0.028	0.82

Abbreviations: $VO2_{peak}$ = peak oxygen uptake, [BG] = blood glucose concentration, LA = left atrium, $VO2/HR_{peak}$ = oxygen pulse, RER_{peak} = respiratory exchange ratio at peak exercise, VO_2/W_{peak} = ratio of oxygen uptake to cycling load at peak exercise

5. Discussion

No significant differences could be observed in cardiac function and exercise tolerance in T1DM as opposed to healthy controls, except in RER at peak exercise. A higher mean [BG] however seems to be significantly correlated with a lower VO_{2peak}. Greater total time in hypoglycemic state was correlated with a higher VO_2/W_{peak}, indicating that glycemic control is related to exercise tolerance.

Exercise tolerance

No differences in maximal oxygen uptake and maximal load were observed between the participants with T1DM and healthy controls, stating that exercise tolerance was preserved in the tested adolescents with T1DM. This observation is in line with previous research in adolescents with T1DM (Nascimento et al., 2017). However, they extrapolated data from a submaximal testing protocol, which may have been invalid in T1DM patients. Other research has established impairments in oxygen uptake in the diabetic population. VO_{2peak} was found to be significantly lower in T1DM in both adolescents as adults when compared to non-diabetic controls (Komatsu et al., 2005; Turinese et al., 2017). Our findings indicate that being diagnosed with T1DM does not necessarily mean that VO_{2peak} is reduced in adolescents with T1DM, but research has reported impairments in adults. It remains important to note that if not taking the complications into account, impairments more than likely will take place.

However, RER_{peak} significantly lowered in adolescents with T1DM, as opposed to their healthy peers. This is in agreement with previous research in T1DM adults (Turinese et al., 2017) but in disagreement with other studies that examined adolescents with T1DM (Heyman et al., 2012; Wilson et al., 2017). Turinese et al. (2017) suggested that RER_{peak} is related to the substrate selection of the skeletal muscles. A lower RER_{peak} may point towards higher lipid oxidation rates during peak exercise and/or lower carbohydrate oxidation rates. During the incremental part of the maximal exercise test, the aerobic pathways are used for substrate selection, but towards the end a shift to anaerobic and thus to carbohydrate oxidation needs to take place to ensure optimal energy. A compromised oxidative aerobic system has been observed in T1DM as opposed to controls during maximal exercise, with no significant shift in the Krebs cycle metabolites. Higher insulin levels also have been reported due to use of exogenous insulin and may be linked to an

attenuated glycogenolytic response since insulin inhibits glycogen breakdown (Brugnara et al., 2014). Some studies have reported abnormalities in mitochondrial capacity and number in subjects with T1DM. They carefully state that this may be a primary cause of the metabolic inflexibility that occurs in these patients (Morino, Petersen, Shulman, & Shulman, 2006).

RER_{peak} turned out to be negatively correlated with the self-reported physical activity levels. This means that with higher activity levels, participants with T1DM showed a lower RER_{peak}. Further research is needed to investigate this relation. In addition, the first ventilatory threshold (VT1) was significantly higher in T1DM patients when compared to healthy controls, supporting the hypothesis of longer use of lipids during low to moderate intense exercise. In final, a higher VO_2 – workload ratio was found in the T1DM group when compared to healthy controls, meaning that they produced a lower workload with similar oxygen uptake. This indicates they need more oxygen for the work delivered. Turinese et al. (2017) did however not find differences in VO_2/W_{peak} in adults with T1DM versus healthy controls. The VO_2/W peak ratio showed a strong positive correlation with the total time in hypoglycemic state (three months). When the time spent in a hypoglycemic state was longer, the exercise efficiency was lower.

The duration of the disease was examined in relation to outcomes of the CPET parameters. It was found to be moderately correlated with workload, VE_{peak}, VO_{2peak}, VCO_{2peak}, oxygen pulse and the second ventilatory threshold (VT2). It showed a strong correlation with relative oxygen uptake (VO_2/kg_{peak}) and load (W/kg_{peak}) at peak exercise. These were all negatively correlated, meaning the longer the duration of the disease, the higher the impact on the exercise capacity and thus deteriorating the last mentioned.

Furthermore, we investigated if [BG] before starting the maximal cardiopulmonary test had a significant influence on the outcomes of the maximal test. We could not find any significant correlations. This is in agreement with previous research (Stettler et al., 2006), where no differences between starting an exercise test in euglycemic as opposed to a hyperglycemic state were observed.

When looking for possible factors affecting VO_{2peak}, mean [BG] (three months) and VO_{2peak} showed a strong negative correlation. This might suggest that patients with higher overall [BG] and thus poorer glycemic control (higher %HbA1c) had lower VO_2 at peak exercise and thus less

exercise capacity compared to subjects with well controlled T1DM. However, we could not find a significant positive correlation with the time spent in a hyperglycemic state or [HbA1c].

Echocardiography

The TTE showed significant differences in E, with E being higher in the T1DM group when compared to healthy controls. This means that the peak early diastolic velocity was higher, without a significant change in filling pattern (E/A) between both groups. Prior research could not reveal such difference in E (Bradley et al., 2016; Brunvand et al., 2017; Hodzic et al., 2016) in T1DM patients as opposed to controls. One study however reported differences in E in poorly controlled T1DM subjects compared to subjects with good glycemic control and non-diabetic controls, with significantly lower values related to poor control as opposed to good control and controls without T1DM (Caglar Acar, Epcacan, Uner, Ece, & Dogan, 2016). Our pilot study could not confirm a relation between E and [BG] over two weeks or three months. The E/A ratio was not significantly different between both groups, but the ratio was closer to the cut-off value 2 in the T1DM group. In this case, that is not related to a restrictive pattern but to supernormal filling of the LV. This phenomenon is often seen in young and active individuals (Nagueh et al., 2016). No other parameters for diastolic function showed significant differences between the groups, meaning we did not find signs of LVDD in this group, based on group averages. Prevention of the development of these complications seems to be possible and thus important in adolescents with T1DM.

Limitations

The small sample size of this study could be a limitation. However, the power analyses of most of the significant findings are high enough to confirm the strength of these findings.

Conclusion

In conclusion, no differences in cardiac function or exercise tolerance were observed between T1DM adolescents and healthy controls. Clinical recommendations include prevention of these complications. Future research is however needed to fully understand the underlying mechanisms of the development of the complications.

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Appendix

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Table 3
Outcome measures

Category	Outcome measures	unit
Puberty stage	Tanner stage	
Body composition	Body height	cm
	SDS score for height	
	Body mass	kg
	Body mass index	Kg/m^2
	SDS score for body mass index	
	Fat mass	%
Continuous pulmonary gas exchange analysis	VO_{2peak}	l/min
	VCO_{2peak}	l/min
	VE_{peak}	l/min
	BF_{peak}	breaths/min
	RER_{peak}	
	Lowest ventilatory equivalent O_2	
	Lowest ventilatory equivalent CO_2	
	Vt_{peak}	L
	$PETO_{2peak}$	mmHg
	$PETCO_{2peak}$	mmHg
Electrocardiogram	HR_{peak}	bpm
Other	VO_2/HR_{peak}	
	VO_2 VT1	ml/min
	VO_2 VT2	ml/min
	$Load_{peak}$	W
	VO_2/W_{peak}	ml/min*w
	W/kg_{peak}	W/kg
	VO_2/kg_{peak}	ml/min*kg
	OUES	
Glycemic control	[HbA1c]	%
	Mean [BG] over 2 weeks	mg/dl
	Mean [BG] over 3 months	mg/dl
	Total time in hyperglycemic state over 2 weeks	%
	Total time in hyperglycemic state over 3 months	%
	Total time in hypoglycemic state over 2 weeks	%
	Total time in hypoglycemic state over 3 months	%
Physical activity	PAQ-A	
	Movement diary	Peak effort exercise hours/week
TTE	E	cm/sec
	A	cm/sec

	E/A ratio	
	Deceleration time of early filling	ms
	EF	%
	CO	l/min
	E’	cm/sec
	A’	cm/sec
	E/e’ ratio	
	LV septal wall thickness	mm
	LV diameter	mm
	LA diameter	mm

Abbreviations: SDS = standard deviation score, $VO2_{peak}$ = peak oxygen uptake, $VCO2_{peak}$ = peak carbon dioxide output, VE_{peak} = expiratory volume at peak exercise, BF_{peak} = breathing frequency at peak exercise, RER_{peak} = respiratory exchange ratio at peak exercise, Vt_{peak} = tidal volume at peak exercise, $PETO_{2peak}$ = End-tidal tensions of oxygen at peak exercise, $PETCO_{2peak}$ = End-tidal tensions of carbon dioxide at peak exercise, HR_{peak} = heart rate at peak exercise, VO_2/HR_{peak} = oxygen pulse at peak exercise, VT1 = first ventilatory threshold, VT2 = second ventilatory threshold, VO_2/W_{peak} = ratio of oxygen uptake to cycling load at peak exercise, W/kg_{peak} = relative load at peak exercise, $VO2/kg_{peak}$ = relative oxygen uptake at peak exercise, OUES = oxygen uptake efficiency slope, [HbA1c] = concentrations of A1c in hemoglobin, [BG] = blood glucose concentration, PAQ-A = physical activity questionnaire for adolescents, E = peak early diastolic velocity, A = peak late diastolic velocity, EF = ejection fraction, CO = cardiac output, E’ = mitral annulus early diastolic velocity, A’ = mitral annulus late diastolic velocity, LV = left ventricle and LA = left atrium

Table 4
Baseline Characteristics

Parameter	Controls (n=14)	T1DM (n=14)	P-value
Gender			1.000
Male	9	9	
Female	5	5	
Age (years)	14.13 ± 1.48 [13.28;14.98]	14.19 ± 1.76 [13.18;15.21]	0.918
Age (months)	169 ± 18 [159;179]	169 ± 20 [158;181]	0.937
Development stage			0.965
Tanner stage 1 (n)	1	1	
Tanner stage 2 (n)	1	1	
Tanner stage 3 (n)	4	2	
Tanner stage 4 (n)	3	5	
Tanner stage 5 (n)	4	5	
No data	0	1	
Body weight (kg)	57.7 ± 13.4 [50.0;65.5]	57.3 ± 12.6 [50.0;64.5]	0.925
Body height (cm)	167.9 ± 8.5 [163.0;172.8]	166.6 ± 5.5 [166.6;169.8]	0.655
Body height SDS	1.01 ± 0.78 [0.56;1.03]	0.54 ± 0.93 [-0.00;1.07]	0.154
BMI (kg/m²)	20.32 ± 3.92 [18.05;22.58]	20.56 ± 4.03 [18.24;22.89]	0.613
BMI SDS	0.16 ± 0.85 [-0.33;0.66]	0.26 ± 0.91 [-0.27;0.78]	0.782
Body fat (%)	17.5 ± 9.5 [12.0;22.9]	21.7 ± 7.5 [17.4;26.0]	0.202
PAQ-A	2.45 ± 0.48 [2.17;2.72]	2.72 ± 0.55 [2.41;3.04]	0.165

Abbreviations: BMI = body mass index, SDS = standard deviation score, PAQ-A = physical activity questionnaire for adolescents

Table 5
Parameters CPET

Parameters	Controls (n= 14)	T1DM (n=14)	P-value	Power
$Load_{peak}$ (W)	181 ± 35 [160;201]	170 ± 32[152;189]	0.408	0.13
HR_{peak} (bpm)	186 ± 10 [180;192]	192 ± 6 [189;196]	0.066	0.47
VE_{peak} (l/min)	79.6 ± 14.2 [71.4;87.8]	80.7 ± 21.9 [68.1;93.4]	0.836	0.05
BF_{peak} (breaths/min)	47 ± 12 [40;54]	43 ± 10 [37;48]	0.295	0.15
VO_{2peak} (ml/min)	2160 ± 502 [1870;2449]	2370 ± 443 [2115;2627]	0.073	0.20
VCO_2 peak (ml/min)	2669 ± 551 [2350;2987]	2720 ± 512 [2425;3016]	0.798	0.06
RER_{peak}	1.24 ± 0.06 [1.21;1.27]	1.15 ± 0.08 [1.11;1.20]	**0.004***	0.90
Vt_{peak} (l)	1.76 ± 0.39 [1.53;1.98]	1.93 ± 0.46 [1.66;2.19]	0.462	0.17
PET CO_{2peak} (mmHg)	37 ± 5 [34;40]	39 ± 5 [36;42]	0.188	0.17
PET O_{2peak} (mmHg)	118 ± 6 [115;122]	116 ± 7 [112;120]	0.342	0.12
VO_2/HR_{peak}	11.61 ± 2.59 [10.12;13.11]	11.57 ± 2.62 [10.06;13.09]	0.783	0.05
VO_2/W_{peak} (ml/min*W)	11.91 ± 0.73 [11.48;12.33]	13.95 ± 1.10 [13.32;14.59]	**<0.001***	1.00
W/Kg_{peak}	3.15 ± 0.56 [2.83;3.47]	3.07 ± 0.70 [2.67;3.47]	0.732	0.09
VO_2/Kg_{peak} (ml/min*kg)	37.73 ± 8.14 [33.04;42.43]	42.95 ± 10.94 [36.64;49.27]	0.164	0.27
VO_2 VT1 (ml/min)	1203.55 ± 298.61 [1002.94;1404.15]	1410.25 ± 394.26 [1195.75;1660.75]	**0.026***	0.31
VO_2 VT2 (ml/min)	1775.73 ± 514.66 [1429.97;2121.48]	1943.83 ± 437.90 [1665.61;2222.06]	0.157	0.14
OUES	2219 ± 483 [1927;2510]	2254 ± 372 [2029;2478]	0.836	0.05
Lowest Ventilatory equivalent VCO_2	23.86 ± 2.25 [22.57;25.16]	23.36 ± 2.30 [22.03;24.69]	0.566	0.09
Lowest Ventilatory equivalent VO_2	20.61 ± 2.98 [18.89;22.33]	18.76 ± 2.10 [17.55;19.98]	0.112	0.43

Abbreviations: HR_{peak} = heart rate at peak exercise, VE_{peak} = expiratory volume at peak exercise, BF_{peak} = breathing frequency at peak exercise, $VO2_{peak}$ = peak oxygen uptake, $VCO2_{peak}$ = peak carbon dioxide output, RER_{peak} = respiratory exchange ratio at peak exercise, Vt_{peak} = tidal volume at peak exercise, $PETO_{2peak}$ = End-tidal tensions of oxygen at peak exercise, $PETCO_{2peak}$ = End-tidal tensions of carbon dioxide at peak exercise, VO_2/HR_{peak} = oxygen pulse at peak exercise, VO_2/W_{peak} = ratio of oxygen uptake to cycling load at peak exercise, W/kg_{peak} = relative load at peak exercise, $VO2/kg_{peak}$ = relative oxygen uptake at peak exercise, VT1 = first ventilatory threshold, VT2 = second ventilatory threshold and OUES = oxygen uptake efficiency slope

Table 6
Parameters TTE

Parameters	Controls (n= 10)	T1DM (n=10)	P-value	Power
E (cm/sec)	79.20 ± 9.65 [72.30;86.10]	93.00 ± 16.95 [80.87;105.13]	**0.031***	0.54
A (cm/sec)	44.10 ± 8.62 [37.93;50.27]	47.30 ± 7.12 [42.21;52.39]	0.377	0.14
E/A ratio	1.88 ± 0.55 [1.49;2.28]	1.97 ± 0.30 [1.75;2.18]	0.687	0.07
Deceleration time of early filling (ms)	147.30 ± 27.98 [127.28;167.32]	140.23 ± 28.67 [119.72;138.61]	0.583	0.08
E/e' ratio	7.70 ± 1.42 [6.69;8.71]	8.15 ± 1.90 [6.79;9.51]	0.820	0.09
CO (l/min)	4.97 ± 0.88 [4.29;5.64]	4.60 ± 1.22 [3.73;5.47]	0.469	0.11

Abbreviations: E = peak early diastolic velocity, A = peak late diastolic velocity and CO = cardiac output

Table 7
The relation between glycemic control or physical activity and exercise tolerance

Parameter 1	Parameter 2	Correlation coefficient	P-value	Power
VO_{2peak} (ml/min)	[HbA1C] (%)	-0.298	0.300	0.19
	Mean [BG] over 2 weeks (mg/dl)	-0.368	0.330	0.19
	Mean [BG] over 3 months (mg/dl)	-0.799	**0.017***	0.76
	Total time in hyperglycemic state over 2 weeks (%)	-0.077	0.833	0.06
	Total time in hyperglycemic state over 3 months (%)	-0.629	0.130	0.39
	Total time in hypoglycemic state over 2 weeks (%)	-0.373	0.288	0.19
	Total time in hypoglycemic state over 3 months (%)	0.233	0.615	0.08
	Total time in euglycemic state over 2 weeks (%)	0.145	0.689	0.07
	Total time in euglycemic state over 3 months (%)	0.514	0.238	0.24
	PAQ-A	0.256	0.376	0.15
	Peak exercise hours/week	0.187	0.540	0.08
$Load_{peak}$ (W)	[HbA1C] (%)	-0.352	0.217	0.25
	Mean [BG] over 2 weeks (mg/dl)	-0.528	0.144	0.36
	Mean [BG] over 3 months (mg/dl)	-0.772	**0.025***	0.82
	Total time in hyperglycemic state over 2 weeks (%)	-0.211	0.559	0.09
	Total time in hyperglycemic state over 3 months (%)	-0.723	0.067	0.61
	Total time in hypoglycemic state over 2 weeks (%)	-0.579	0.079	0.51
	Total time in hypoglycemic state over 3 months (%)	-0.214	0.645	0.08
	Total time in euglycemic state over 2 weeks (%)	0.318	0.370	0.16
	Total time in euglycemic state over 3 months (%)	0.720	0.068	0.060
	PAQ-A	0.079	0.787	0.06
	Peak exercise hours/week	0.208	0.495	0.11

Abbreviations: VO_{2peak} = oxygen uptake at peak exercise, [HbA1c] = concentrations of A1c in hemoglobin, [BG] = blood glucose concentration and PAQ-A = physical activity questionnaire for adolescents

Table 8
The relation between glycemic control or physical activity and cardiac function

Parameter 1	Parameter 2	Correlation coefficient	P-value	Power
E (cm/sec)	[HbA1c]	0.196	0.587	0.09
	Mean [BG] over 3 months (mg/dl)	-0.549	0.338	0.18
	Total time in hyperglycemic state over 3 months (%)	-0.716	0.284	0.23
	PAQ-A	-0.542	0.105	0.43
A (cm/sec)	[HbA1c]	-0.178	0.623	0.08
	Mean [BG] over 3 months (mg/dl)	-0.417	0.484	0.11
	Total time in hyperglycemic state over 3 months (%)	-0.383	0.617	0.08
	PAQ-A	-0.131	0.719	0.07
E/A	[HbA1c]	0.425	0.220	0.26
	Mean [BG] over 3 months (mg/dl)	-0.327	0.591	0.09
	Total time in hyperglycemic state over 3 months (%)	-0.545	0.455	0.13
	PAQ-A	-0.476	0.165	0.33
E' (cm/sec)	[HbA1c]	0.013	0.971	0.05
	Mean [BG] over 3 months (mg/dl)	-0.267	0.665	0.07
	Total time in hyperglycemic state over 3 months (%)	-0.314	0.686	0.07
	PAQ-A	-0.285	0.425	0.13
A' (cm/sec)	[HbA1c]	-0.035	0.929	0.05
	Mean [BG] over 3 months (mg/dl)	0.337	0.663	0.07
	Total time in hyperglycemic state over 3 months (%)	-0.721	0.488	0.11
	PAQ-A	-0.290	0.449	0.12
E/E'	[HbA1c]	0.172	0.635	0.08
	Mean [BG] over 3 months (mg/dl)	-0.479	0.414	0.14
	Total time in hyperglycemic state over 3 months (%)	-0.560	0.440	0.13
	PAQ-A	-0.234	0.515	0.10
CO (l/min)	[HbA1c]	-0.208	0.564	0.09
	Mean [BG] over 3 months (mg/dl)	-0.576	0.310	0.20
	Total time in hyperglycemic state over 3 months (%)	-0.619	0.381	0.16
	PAQ-A	-0.569	0.086	0.49
EF (%)	[HbA1c]	-0.337	0.317	0.19
	Mean [BG] over 3 months (mg/dl)	-0.825	0.175	0.37
	Total time in hyperglycemic state over 3 months (%)	-0.996	0.059	0.87

	PAQ-A	-0.332	0.383	0.15
Deceleration time of early filling (ms)	[HbA1c]	0.022	0.952	0.05
	Mean [BG] over 3 months (mg/dl)	0.222	0.720	0.07
	Total time in hyperglycemic state over 3 months (%)	0.264	0.736	0.06
	PAQ-A	0.756	**0.011***	0.89
Deceleration time of early filling of healthy controls (ms)	PAQ-A	0.190	0.515	0.10
LV septal wall thickness (mm)	[HbA1c]	-0.387	0.269	0.22
	Mean [BG] over 3 months (mg/dl)	-0.658	0.227	0.28
	Total time in hyperglycemic state over 3 months (%)	-0.708	0.292	0.22
	PAQ-A	-0.155	0.670	0.07
LV diameter (mm)	[HbA1c]	0.170	0.639	0.08
	Mean [BG] over 3 months (mg/dl)	-0.446	0.451	0.13
	Total time in hyperglycemic state over 3 months (%)	-0.510	0.490	0.11
	PAQ-A	-0.197	0.585	0.09
LA diameter (mm)	[HbA1c]	0.026	0.944	0.05
	Mean [BG] over 3 months (mg/dl)	-0.306	0.617	0.08
	Total time in hyperglycemic state over 3 months (%)	-0.333	0.667	0.07
	PAQ-A	-0.786	**0.007***	0.94
LA diameter healthy controls (mm)	PAQ-A	-0.313	**0.276**	0.17

Abbreviations: E = peak early diastolic velocity, A = peak late diastolic velocity, E' = mitral annulus early diastolic velocity, A' = mitral annulus late diastolic velocity, CO = cardiac output, EF = ejection fraction, LV = left ventricle, LA = left atrium, [HbA1c] = concentrations of A1c in hemoglobin, [BG] = blood glucose concentration and PAQ-A = physical activity questionnaire for adolescents

Table 9
The relation between exercise tolerance and cardiac function

Parameter 1	Parameter 2	Correlation coefficient	P-value	Power
VO_{2peak} (ml/min)	E (cm/sec)	0.093	0.798	0.06
	A (cm/sec)	-0.594	0.070	0.54
	E/A ratio	0.808	**0.005***	0.97
	E' (cm/sec)	-0.168	0.642	0.08
	A' (cm/sec)	-0.301	0.431	0.14
	E/e' ratio	0.257	0.474	0.12
	Deceleration time of early filling (ms)	-0.310	0.384	0.15
	CO (l/min)	0.431	0.213	0.27
	EF (%)	0.175	0.653	0.08
	LV septal wall thickness (mm)	0.495	0.146	0.35
	LV diameter (mm)	0.453	0.188	0.29
	LA diameter (mm)	0.288	0.419	0.13
$Load_{peak}$ (W)	E (cm/sec)	0.258	0.472	0.12
	A (cm/sec)	-0.380	0.279	0.21
	E/A ratio	0.810	**0.005***	0.97
	E' (cm/sec)	-0.091	0.803	0.06
	A' (cm/sec)	-0.320	0.402	0.14
	E/e' ratio	0.315	0.375	0.15
	Deceleration time of early filling (ms)	-0.401	0.251	0.23
	CO (l/min)	0.453	0.188	0.29
	EF (%)	0.229	0.554	0.09
	LV septal wall thickness (mm)	0.407	0.243	0.24
	LV diameter (mm)	0.587	0.074	0.52
	LA diameter (mm)	0.394	0.261	0.22

Abbreviations: VO_{2peak} = oxygen uptake at peak exercise, E = peak early diastolic velocity, A = peak late diastolic velocity, E' = mitral annulus early diastolic velocity, A' = mitral annulus late diastolic velocity, CO = cardiac output, EF = ejection fraction, LV = left ventricle and LA = left atrium

Table 10
Duration of the disease

Parameter 1	Parameter 2	Correlation coefficient	P-value	Power
Duration of the disease (months)	$Load_{peak}$ (W)	-0.544	**0.040***	0.61
	HR_{peak} (beats/min)	0.379	0.181	0.29
	VE_{peak} (l/min)	-0.542	**0.045***	0.60
	BF_{peak} (breaths/min)	-0.393	0.165	0.31
	VO_{2peak} (ml/min)	-0.658	**0.011***	0.85
	VCO_{2peak} (ml/min)	-0.598	**0.024***	0.73
	RER_{peak}	0.244	0.400	0.14
	VT_{peak} (l)	-0.219	0.452	0.12
	Lowest Ventilatory equivalent VCO_2	-0.058	0.844	0.05
	Lowest Ventilatory equivalent VO_2	0.174	0.552	0.09
	PET CO_{2peak} (mmHg)	0.292	0.310	0.18
	PET O_{2peak} (mmHg)	-0.132	0.652	0.07
	VO_2/W_{peak} (ml/min*W)	-0.323	0.260	0.22
	VO_2/HR_{peak}	-0.665	**0.009***	0.86
	VT1 VO_2 (ml/min)	-0.507	0.064	0.53
	VT2 VO_2 (ml/min)	-0.578	**0.049***	0.68
	VO_2/kg_{peak} (ml/min*kg)	-0.777	**0.001***	0.99
	W/kg_{peak}	-0.771	**0.001***	0.99
	OUES	-0.479	0.097	0.43
	E (cm/sec)	0.224	0.534	0.09
	A (cm/sec)	0.516	0.127	0.35
	E/A ratio	-0.278	0.436	0.12
	Deceleration time of early filling (ms)	0.045	0.901	0.05
	E' (cm/sec)	-0.026	0.944	0.05
	A' (cm/sec)	0.449	0.226	0.26
	E/e'	0.203	0.573	0.08
	CO (l/min)	-0.345	0.329	0.16
	EF (%)	-0.703	**0.035***	0.72

Abbreviations: HR_{peak} = heart rate at peak exercise, VE_{peak} = expiratory volume at peak exercise, BF_{peak} = breathing frequency at peak exercise, $VO2_{peak}$ = peak oxygen uptake, $VCO2_{peak}$ = peak carbon dioxide output, RER_{peak} = respiratory exchange ratio at peak exercise, Vt_{peak} = tidal volume at peak exercise, $PETO_{2peak}$ = End-tidal tensions of oxygen at peak exercise, $PETCO_{2peak}$ = End-tidal tensions of carbon dioxide at peak exercise, VO_2/W_{peak} = ratio of oxygen uptake to cycling load at peak exercise, VO_2/HR_{peak} = oxygen pulse at peak exercise, VT1 = first ventilatory threshold, VT2 = second ventilatory threshold, $VO2/kg_{peak}$ = relative oxygen uptake at peak exercise, W/kg_{peak} = relative load at peak exercise, OUES = oxygen uptake efficiency slope, E = peak early diastolic velocity, A = peak late diastolic velocity, E' = mitral annulus early diastolic velocity, A' = mitral annulus late diastolic velocity, CO = cardiac output and EF = ejection fraction

Table 11
Relation between [BG] before maximal exercise and CPET parameters

Parameter 1	Parameter 2	Correlation coefficient	P-value	Power
[BG] before exercise	$Load_{peak}$ (W)	0.116	0.694	0.07
	HR_{peak} (beats/min)	0.304	0.290	0.20
	VE_{peak} (l/min)	0.104	0.723	0.07
	BF_{peak} (breaths/min)	0.119	0.686	0.07
	VO_{2peak} (ml/min)	0.120	0.682	0.07
	VCO_{2peak} (ml/min)	0.155	0.596	0.08
	RER_{peak}	0.111	0.705	0.07
	VT_{peak} (l)	-0.020	0.945	0.05
	Lowest Ventilatory equivalent VCO_2	-0.319	0.267	0.21
	Lowest Ventilatory equivalent VO_2	0.157	0.593	0.09
	PET O_{2peak} (mmHg)	0.152	0.605	0.08
	PET CO_{2peak} (mmHg)	-0.286	0.321	0.18
	VO_2/W_{peak} (ml/min*W)	-0.026	0.929	0.05
	VO_2/HR_{peak}	-0.064	0.827	0.06
	VT1 VO_2 (ml/min)	-0.080	0.787	0.06
	VT2 VO_2 (ml/min)	-0.224	0.485	0.12
	VO_2/kg_{peak} (ml/min*kg)	-0.080	0.787	0.06
	W/kg_{peak}	-0.077	0.793	0.06
	OUES	0.070	0.819	0.06

Abbreviations: HR_{peak} = heart rate at peak exercise, VE_{peak} = expiratory volume at peak exercise, BF_{peak} = breathing frequency at peak exercise, $VO2_{peak}$ = peak oxygen uptake, $VCO2_{peak}$ = peak carbon dioxide output, RER_{peak} = respiratory exchange ratio at peak exercise, Vt_{peak} = tidal volume at peak exercise, $PETO_{2peak}$ = End-tidal tensions of oxygen at peak exercise, $PETCO_{2peak}$ = End-tidal tensions of carbon dioxide at peak exercise, VO_2/W_{peak} = ratio of oxygen uptake to cycling load at peak exercise, VO_2/HR_{peak} = oxygen pulse at peak exercise, VT1 = first ventilatory threshold, VT2 = second ventilatory threshold, $VO2/kg_{peak}$ = relative oxygen uptake at peak exercise, W/kg_{peak} = relative load at peak exercise and OUES = oxygen uptake efficiency slope

Table 12
Supplementary correlations

Parameter 1	Parameter 2	Correlation coefficient	P-value	Power
RER_{peak}	[HbA1C] (%)	0.094	0.749	0.06
	Mean [BG] over 2 weeks (mg/dl)	-0.151	0.698	0.07
	Mean [BG] over 3 months (mg/dl)	0.296	0.476	0.12
	Total time in hyperglycemic state over 2 weeks (%)	-0.239	0.507	0.11
	Total time in hyperglycemic state over 3 months (%)	0.084	0.858	0.05
	Total time in hypoglycemic state over 2 weeks (%)	-0.329	0.354	0.16
	Total time in hypoglycemic state over 3 months (%)	-0.649	0.115	0.45
	Total time in euglycemic state over 2 weeks (%)	0.301	0.398	0.14
	Total time in euglycemic state over 3 months (%)	0.097	0.836	0.06
	PAQ-A	-0.620	**0.018***	0.77
	Peak exercise hours/week	-0.029	0.925	0.05
VO_2/W_{peak} (ml/min*W)	[HbA1C] (%)	0.002	0.995	0.05
	Mean [BG] over 2 weeks (mg/dl)	0.126	0.746	0.06
	Mean [BG] over 3 months (mg/dl)	-0.224	0.595	0.09
	Total time in hyperglycemic state over 2 weeks (%)	0.263	0.462	0.12
	Total time in hyperglycemic state over 3 months (%)	0.023	0.961	0.05
	Total time in hypoglycemic state over 2 weeks (%)	0.536	0.110	0.42
	Total time in hypoglycemic state over 3 months (%)	0.808	**0.028***	0.82
	Total time in euglycemic state over 2 weeks (%)	-0.369	0.294	0.20
	Total time in euglycemic state over 3 months (%)	-0.238	0.607	0.08
	PAQ-A	0.520	0.056	0.55
	Peak exercise hours/week	-0.052	0.866	0.05
VO_2 VT1 (ml/min)	[HbA1C] (%)	-0.016	0.958	0.05
	Mean [BG] over 2 weeks (mg/dl)	0.096	0.806	0.06
	Mean [BG] over 3 months (mg/dl)	-0.432	0.285	0.21

	Total time in hyperglycemic state over 2 weeks (%)	0.187	0.604	0.08
	Total time in hyperglycemic state over 3 months (%)	-0.174	0.710	0.07
	Total time in hypoglycemic state over 2 weeks (%)	-0.380	0.297	0.21
	Total time in hypoglycemic state over 3 months (%)	0.429	0.337	0.18
	Total time in euglycemic state over 2 weeks (%)	-0.107	0.769	0.06
	Total time in euglycemic state over 3 months (%)	0.044	0.925	0.05
	PAQ-A	0.082	0.779	0.06
	Peak exercise hours/week	-0.099	0.748	0.06
E (cm/sec)	[HbA1C] (%)	0.196	0.587	0.09
	Mean [BG] over 2 weeks (mg/dl)	0.271	0.604	0.08
	Mean [BG] over 3 months (mg/dl)	-0.549	0.338	0.18
	Total time in hyperglycemic state over 2 weeks (%)	0.233	0.614	0.08
	Total time in hyperglycemic state over 3 months (%)	-0.716	0.284	0.23
	Total time in hypoglycemic state over 2 weeks (%)	-0.628	0.131	0.41
	Total time in hypoglycemic state over 3 months (%)	-0.708	0.292	0.22
	Total time in euglycemic state over 2 weeks (%)	-0.088	0.851	0.05
	Total time in euglycemic state over 3 months (%)	0.723	0.277	0.23
	PAQ-A	-0.542	0.105	0.60
	Peak exercise hours/week	-0.321	0.400	0.14

<u>Abbreviations</u>: RERpeak = respiratory exchange ratio at peak exercise, VO_2/W_{peak} = ratio of oxygen uptake to cycling load at peak exercise, VO_2 VT1 = oxygen uptake at first ventilatory threshold, E = peak early diastolic velocity, [HbA1c] = concentrations of A1c in hemoglobin, [BG] = blood glucose concentration and PAQ-A = physical activity questionnaire for adolescents

List of abbreviations (alphabetical order)

- A: Peak late diastolic velocity
- A': Mitral annulus late diastolic velocity
- BF: Breathing frequency
- [BG]: Blood glucose concentration
- BMI: Body mass index
- CO: Cardiac output
- CPET: Cardiopulmonary exercise test
- E: Peak early diastolic velocity
- E': Mitral annulus early diastolic velocity
- EF: Ejection fraction
- [HbA1c]: Concentrations of A1c in hemoglobin
- HR: Heart rate
- LA: Left atrium
- LV: Left ventricular
- LVDD: Left ventricular diastolic dysfunction
- OUES: Oxygen uptake efficiency slope
- PAQ-A: Physical activity questionnaire for adolescents
- $PETO_2$: End-tidal tensions of oxygen
- $PETCO_2$: End-tidal tensions of carbon dioxide
- RER: Respiratory exchange ratio
- SDS: Standard deviation score
- T1DM: Type 1 diabetes mellitus
- TTE: Trans-thoracic echocardiography
- VE: Expiratory volume
- VO_2: Amount of oxygen uptake
- VO_2/HR: Oxygen pulse
- VO_2/kg: Relative oxygen uptake
- VO_2/W: Ratio of oxygen uptake to cycling load, work rate efficiency
- VCO_2: Amount of carbon dioxide output

- Vt: Tidal volume
- VT1: First ventilatory threshold
- VT2: Second ventilatory threshold
- W/kg: Relative load

PAQ-A questionnaire

f. Vlaamse versie PAQ-A: middelbare school

Naam : _____ Leeftijd:_____

Geslacht : M / V Studiejaar:_____

Met deze vragenlijst willen we een beeld krijgen van het niveau van jouw fysieke activiteiten van **de voorbije 7 dagen** (dus de voorbije week). Met deze activiteiten bedoelen we sporten of dansen waarvan je gaat zweten of waarbij je benen moe aanvoelen of spelletjes waardoor je sneller gaat ademen, zoals tikkertje, touwtjespringen, rennen, klimmen en andere.

Onthoud het volgende:

1. Dit is geen test! Er zijn dus geen juiste of foute antwoorden.
2. Gelieve de vragen zo eerlijk en correct mogelijk in te vullen. Dit is voor ons zeer belangrijk.

---

1) Fysieke activiteit in je vrije tijd : Heb je één of meer van de volgende activiteiten in de voorbije 7 dagen (voorbije week) beoefend? Zo ja, hoeveel keer? (Kleur per rij slechts 1 bolletje in)

	Niet	1-2	3-4	5-6	7 keer of meer
Touwspringen	O	O	O	O	O
Tennis	O	O	O	O	O
In-line skating	O	O	O	O	O
Tikkertje spelen	O	O	O	O	O
Wandelen als sport	O	O	O	O	O
Fietsen	O	O	O	O	O
Joggen of rennen	O	O	O	O	O
Atletiek	O	O	O	O	O
Zwemmen	O	O	O	O	O
Baseball, honkbal	O	O	O	O	O
Dansen	O	O	O	O	O
Rugby	O	O	O	O	O
Badminton	O	O	O	O	O
Skateboarden	O	O	O	O	O
Voetbal	O	O	O	O	O
Hockey	O	O	O	O	O
Volleybal	O	O	O	O	O
Gevechtssporten	O	O	O	O	O
Basketbal	O	O	O	O	O
IJsschaatsen	O	O	O	O	O
Paardrijden	O	O	O	O	O
Turnen	O	O	O	O	O
Andere	O	O	O	O	O
	O	O	O	O	O

2) Hoe vaak ben je de voorbije 7 dagen erg actief geweest *tijdens de turnlessen* (actief spelen, lopen, springen, werpen)? Kleur slechts één bolletje.

Ik doe niet mee tijdens de turnlessen ..... O
Bijna nooit ..... O
Soms ..... O
Bijna altijd ..... O
Altijd ..... O

3) Wat heb je in de voorbije 7 dagen meestal gedaan *tijdens de lunchpauze*, behalve het eten van je middagmaal? Kleur slechts één bolletje.

Zitten (praten, lezen, huiswerk maken) ..... O
Rechtstaan of rondwandelen ..... O
Een beetje rondlopen of spelen ..... O
Redelijk veel rondlopen of spelen ..... O
Bijna steeds rondlopen of hevig spelen ..... O

4) Hoeveel keer in de voorbije 7 dagen heb je, *onmiddellijk na school*, gesport, gedanst of een spel gespeeld waarbij je zeer actief was? Kleur slechts één bolletje.

Geen enkele keer ..... O
1 keer de afgelopen week ..... O
2 of 3 keer afgelopen week ..... O
4 keer de afgelopen week ..... O
5 keer de afgelopen week ..... O

5) Hoeveel keer in de voorbije 7 dagen heb je '*s avonds* gesport, gedanst of een spel gespeeld waarbij je zeer actief was? Kleur slechts één bolletje.

Geen enkele keer ..... O
1 keer de afgelopen week ..... O
2 of 3 keer afgelopen week ..... O
4 keer de afgelopen week ..... O
5 keer de afgelopen week ..... O

6) Hoeveel keer heb je *in het voorbije weekend* gesport, gedanst of een spel gespeeld waarbij je zeer actief was? Kleur slechts één bolletje.

Geen enkele keer ..... O
1 keer de afgelopen week ..... O
2 of 3 keer afgelopen week ..... O
4 keer de afgelopen week ..... O
5 keer de afgelopen week ..... O

7) Welk van de volgende stellingen beschrijft jou het best voor de voorbije 7 dagen? Lees eerst alle 5 de stellingen alvorens je één antwoord kiest dat het beste bij je past.
(Omcirkel de letter van één stelling)

A. Zelden of nooit heb ik in mijn vrije tijd fysieke activiteiten gedaan zoals sporten, lopen, zwemen, fietsen, aerobics,…
B. Soms (1-2 keer de voorbije week) heb ik fysieke activiteiten gedaan in mijn vrije tijd (zoals sporten, lopen, zwemmen, fietsen, aerobics,…)
C. Frequent (3-4 keer de voorbije week) heb ik fysieke activiteiten gedaan in mijn vrije tijd
D. Heel frequent (5-6 keer de voorbije week) heb ik fysieke activiteiten gedaan in mijn vrije tijd
E. Zeer frequent (7 keer of meer de voorbije week) heb ik fysieke activiteiten gedaan in mijn vrije tijd

8) Duidt aan hoe vaak je aan fysieke activiteit deed (zoals sporten, spelen, dansen of iets anders) voor elke dag van de voorbije week.

	Niet	Een beetje	Medium	Vaak	Bijna altijd
Maandag	O	O	O	O	O
Dinsdag	O	O	O	O	O
Woensdag	O	O	O	O	O
Donderdag	O	O	O	O	O
Vrijdag	O	O	O	O	O
Zaterdag	O	O	O	O	O
Zondag	O	O	O	O	O

9) Ben je de voorbije week ziek geweest of heb je iets speciaals gedaan waardoor je jouw normale fysieke activiteiten niet kon doen?

Ja ..... O
Nee ..... O

Zo ja, wat was de oorzaak? .....

Consultations with promotor

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Campus Diepenbeek | Agoralaan gebouw D | BE 3590 Diepenbeek
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UHASSELT

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
25/09/2017	Startoverleg MPZ	Promotor: Copromotor: Student(e): Student(e): DeVriendt
8/01/2018	Verloven PAQ - A. teksten inleiding en protocol	Promotor: Copromotor: Student(e): Student(e): DeVriendt
15/01/2018	● afspraken maken omtrent organisatie	Promotor: Copromotor: Student(e): Student(e): DeVriendt
23/01/2018	Bespreken protocol	Promotor: Copromotor: Student(e): Student(e): DeVriendt
2/02/2018	Verleg protocol met promotor + copromotor	Promotor: Copromotor: Student(e): Student(e): DeVriendt
14/02/2018	Bespreking organisatie van testdag	Promotor: Copromotor: Student(e): Student(e): DeVriendt
16/03/2018	Verleg met promotor	Promotor: Copromotor: Student(e): Student(e): DeVriendt
27/03/2018	Verleg met copromotor	Promotor: Copromotor: Student(e): Student(e): DeVriendt
18/05/2018	Verleg over statistische analyse	Promotor: Copromotor: Student(e): Student(e): DeVriendt
22/05/2018	Verleg over Statistische analyse deel 2	Promotor: Copromotor: Student(e) Student(e): DeVriendt

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Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Cardiac dysfunction in adolescents with type 1 diabetes: contribution of daily-life glucoregulation and impact on cardiorespiratory exercise capacity

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2018**

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Voor akkoord,

De Vriendt, Friedelinde **Indesteege, Jonas**